Amendments to the Drawings:

The attached sheets of drawings includes changes to Fig. 1 to Fig. 9. These sheets replace the original sheets including Fig. 1 to Fig. 9.

The Applicant provides herewith new corrected drawings in compliance with the requirements of 37 C.F.R. § 1.121(d). The Applicant has amended the drawings so that the text is clearer and will reproduce well for publication. The Applicant has complied with the Examiner's request to provide a clearer image of Figure 6. With regard to Figure 1, the Figure originally filed in PCT/GB02/01137 included a "G1" rather than "M1". The change from "G1" to "M1" was inadvertently introduced when formal drawings were filed to meet formalities objections raised by the PCT Receiving Office. In fact, as would be appreciated by one skilled in the art of flow cytometry, the marker M1 in Figure 1 identifies cells that are in the G1 phase of the cell cycle. As such, the Applicant has amended Figure 1 to replace the designation "M1" with the correct identifier, "G1" to accurately conform with the form of the Figure as originally filed in the PCT. This amendment adds no new matter.

Attachment: Replacement Sheets

REMARKS / ARGUMENTS

Upon entry of the present amendments, claims 1-18 are pending in the application. Claims 19-29 are withdrawn from consideration. The foregoing amendments were made without any intention to abandon any subject matter, but with the intention that one or more claims of the same, lesser, or greater scope may be pursued in a later application or in a continuation, continuation-in-part, or divisional application. The present amendment does not add new matter.

Objections

Priority

The Applicant provides herewith a certified copy of GB 0106051.6 application pursuant to the requirement of 35 U.S.C. § 119(b).

Drawings

The Applicant provides herewith new corrected drawings in compliance with the requirements of 37 C.F.R. § 1.121(d). The Applicant has amended the drawings so that the text is clearer and will reproduce well for publication. The Applicant has complied with the Examiner's request to provide a clearer image of Figure 6. With regard to Figure 1, the Figure originally filed in PCT/GB02/01137 included a "G1" rather than "M1". The change from "G1" to "M1" was inadvertently introduced when formal drawings were filed to meet formalities objections raised by the PCT Receiving Office. In fact, as would be appreciated by one skilled in the art of flow cytometry, the marker M1 in Figure 1 identifies cells that are in the G1 phase of the cell cycle. As such, the Applicant has amended Figure 1 to replace the designation "M1" with the correct identifier, "G1" to accurately conform with the form of the Figure as originally filed in the PCT. This amendment adds no new matter. The Applicant respectfully requests withdrawal of the Examiner's objections to the drawings as they have been amended in accordance with the Examiner's suggestions as well as the requirements of 37 C.F.R. § 1.121(d).

Specification

The Applicant has attended to the Examiner's objections regarding informalities by amending the specification in accordance with the Examiner's suggestions. The Applicant has also amended the specification to correct obvious typographical errors.

Claim objections

The Applicant has amended the claim set to appear in the form of a single sentence by amending the claims to recite --I claim:-- at the head of the claim set as required by the Examiner. Claim 1 has been amended to include a period at the end. Claims 7-10 and 13-18 so that multiple dependent claims do not depend from any other multiple dependent claim as detailed in M.P.E.P. § 608.01(n). The Applicant respectfully requests withdrawal of the Examiner's objections to the claims as they have been amended in accordance with the Examiner's suggestions.

Claim Rejections -35 U.S.C. § 112, first paragraph

The Examiner rejected claims 1-6 and 11-12 pursuant to 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. Specifically, the Examiner alleges that the claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The Examiner has calls into question whether the inventor has truly determined whether the cell cycle defect observed in non-neuronal cells of AD patients is a defect in the G1/S checkpoint.
In particular, in paragraph 14 the Examiner contends that the experimental data presented in the application as filed do not support the conclusion that lymphocytes from AD patients respond differently to agents (*e.g.*, rapamicin and H_2O_2) than controls and patients suffering other dementias. The Applicant notes that the Examiner raises this objection regarding adequate written description in the context of original claims where there is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976).

As detailed in M.P.E.P. § 2163.02 (Standard for Determining Compliance With the Written Description Requirement), the essential question to be addressed in a description requirement issue is if, "the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). To meet the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. An applicant shows possession of the claimed invention by describing

the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

The Applicant traverses the Examiner's rejection of claims 1-6 and 11-12 pursuant to 35 U.S.C. § 112, first paragraph because the applicant has described distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, *e.g.*, *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it"). The claims at issue are drawn to a method of screening patients for Alzheimer's disease (AD) where the presence of a G1/S checkpoint defect in non-neuronal cells indicates that the patient has AD. Office Action at ¶ 13. The Examiner questions the conclusion that the cell cycle defect is due to a G1/S checkpoint defect based on the differences observed between the responses of cells from different patient groups when comparing rapamycin and H_2O_2 to doxorubicin. Office Action at ¶ 16. Specifically, the Examiner alleges that the studies of the instant application lack for proper experimental control of age and thus, it is "impossible to come to the conclusion that the defect is definitively at the G1/S checkpoint." Office Action at ¶ 15, lines 12-14. That is, the Examiner reasons that the specification lacks support for the above-referenced claims because the studies allegedly fail to demonstrate possession of the invention as claimed where age has not been controlled. The Examiner's reasoning is flawed because age correction is not absolutely required due to the design of the experiment illustrated in Figure 2. Accordingly, the inventor's results validly confirm the presence of a regulatory defect at G1/S in AD patients as detailed below.

The results presented in Figure 2 illustrate the *relative* lengthening of the G1 phase under the effects of a G1/S inhibitor such as rapamicin. In the context of this investigation, a value of 100 (on the Y axis) means that the G1 phase of the cell cycle became twice as long as it was before treatment with rapamicin. Accordingly, if patient lymphocytes spent 10 hours in the G1 phase prior to treatment with rapamicin, after such treatment lymphocytes from the same patient will spend twenty hours in the G1 phase. This result would indicate that in the presence of inhibitor (rapamicin) the transition point (G1/S) is functional and stops progression from G1. However, if the same patient lymphocytes exhibit only a 50% response, it would mean that the G1 phase is lengthened only to 15 hours following rapamicin treatment. This would indicate that the G1/S transition checkpoint control is less efficient, as rapamicin cannot elicit an adequate

response. In this set of experiments therefore the closer the measure of *relative* lengthening is to 100 the better the result for the patient (*i.e.* absence of regulatory defect at G1/S).

The inventor has observed that this *relative* lengthening of G1 (*i.e.*, response to G1/S inhibition) is significantly reduced in AD patients (with or without other pathologies) as well as in the pre-clinical stages of Alzheimer's Disease (pre-AD group) relative to controls and other dementias (DNOS). This is illustrated in Figure 2 (first panel). The age correction reduced the standard errors in the group measurements as expected, but did not alter the differences between groups, as shown in Figure 2, right panel.

In the context of this particular experiment the age correction is not vital, due to the fact that the measured parameter is a *relative* measurement. If one were to say that the G1 phase is lengthened by a particular amount of time, *i.e.*, lengthened by five hours instead of the expected 10 hours, then age correction of the result would indeed be necessary, since age influences the length of the G1 phase making it generally longer. However, the inventor's experiment relies on a *relative* measure, for which age correction is not necessary. By way of example, the results of such an experiment might indicate that the G1 phase is lengthened by 50% instead of the expected 100%. This relative measure (50%) is identical in a 60 year old AD patient (where the 50% relative lengthening means a G1 phase of 10+5 hours instead of ten hours) and in a 75 year old AD patient (where a relative lengthening of 50% means 15 + 7.5 hours instead of the expected 15 hour G1 phase). Thus, measurement of relative lengthening depends entirely on the actions of the drug under test on the cell cycle and is independent of age.
Age correction was performed purely in order to reassure the reader that indeed the inventor's results are not skewed by age. The fact that the differences between patient groups do not change after the age correction (*i.e.*, the trend of difference between the two panels of Figure 2 are identical) indicate that the inventors reasoning on the requirement for age correction was correct.

The Examiner also questions the treatment of data presented for DNOS cells. Office Action at ¶ 16. Specifically, the Examiner alleges that the studies presented in Figures 3-5 of the instant application would incorrectly lead the "skilled artisan to conclude that these [DNOS] cells were derived from an AD patient." Office Action at ¶ 16, lines 7-8. That is, the Examiner reasons that the specification lacks support for the above-referenced claims because the studies in Figures 3-5 allegedly fail to demonstrate possession of the invention as claimed. The Examiner's reasoning is flawed because the Examiner fails to appreciate the differences in the experimental designs between the experiments presented in Figure 2 and the studies presented in Figures 3-5. Indeed, as detailed below, the results of experiments presented in Figure 2 and the results of

the experiments presented in Figures 3-5 are both consistent with the Applicants assertion that the cellular defect is at the G1/S checkpoint.

Figures 3 to 5 illustrate the result of a second set of experiments that are very different in nature, measuring a different outcome of cell cycle manipulation at different checkpoints. In this approach the inventor measured the surviving cell cycle populations after cell cycle manipulation based on an MTT proliferation assay. In the context of these experiments a value of 100% on the Y axis means that the intervention (*i.e.*, drug treatment) did not alter the cell numbers in culture. This could be for one of two reasons: 1) The cells do not change their proliferation characteristics and there is no change in cell death either; or 2) Changes in cell proliferation are compensated by changes in cell death (*i.e.*, increased proliferation with increased cell death, or slower proliferation with less cell death). A result of 50% on the Y axis would indicate that the intervention (drug treatment) reduced the number of viable cells to half of their normal numbers. This could be due to the following effects: 1) The cell have slowed down in their proliferation, *e.g.*, due to a cell cycle effect at G1/S or G2; or 2) The cells are dying in large numbers. The experimental design used was such that interventions (drug treatment) would not affect cell deaths in the cultures. Accordingly, variations in cell numbers as a result of the intervention were entirely due to the effects on the cell cycle. However, because the resulting cell numbers are inversely related to the length of G1, in this experimental paradigm a value of 100% (meaning no change in proliferation) is an adverse result for the individual under test, because it indicates the lack of G1/S (or G2) checkpoint control, whilst a result of 50% indicates a robust inhibition of cell division and good working cell cycle checkpoints.

The experimental set up used in the experiments illustrated in Figures 3 to 5 requires age correction because the numbers of dividing cells in any lymphocyte culture will depend very much on the age of the individual under test. The effects of the age correction on these experiments are clearly visible from the differences in the trends shown in Figures 3 to 5. Based on the above analysis, using the same drug one would expect an inverse relationship between the results of the two experimental set ups illustrated in Figure 2 and in Figures 3 to 5. In other words, high measurements (near 100) in the first experimental paradigm would be associated with low experimental measurements in the second paradigm, assuming that the second method is sensitive enough to measure cell cycle effects and is not affected by other factors related to the disease conditions analysed.

This inverse relationship between G1 change in the first experiment (Figure 2) and cell numbers in the second experiment (Figure 3) is observed in the case of rapamicin in all patients with the exception of the DNOS (dementia not otherwise specified) patients. This would indicate

that although the second experimental approach *does* differentiate between controls and AD patients, the assay methodology used (MTT assay) *does not* offer as clear differentiation between AD and the other dementias as is obtained with the first experimental approach. The lower sensitivity of the MTT assay as opposed to flow cytometry is discussed in the application as filed, particularly on page 26, lines 19 to 33. It is to be emphasised, however, that the relatively low sensitivity of the MTT assay does not call into question the validity of the inventor's findings of the existence of a regulatory defect at the G1/S transition in Alzheimer's patients as evidenced by the flow cytometry experiments.

The MTT assay is based on measurement of mitochondrial enzyme activity. This assay can be used to estimate cell numbers, because every living cell has approximately equal amounts of active mitochondrial enzymes, unless the number and/or function of mitochondria is affected by a disease state. In fact, mitochondrial function *is* known to be affected in some dementia disorders (oxidative stress theory). Because by definition the DNOS and possible AD patient groups were heterogeneous groups of patients that may have many different disease conditions other than Alzheimer's, the inventor restricted the discussion of the second set of experiments based on the MTT assay with doxorubicin and H_2O_2 to the AD, pre-AD and control patient groups where the MTT assay correctly reflects the results of flow cytometry, which is the standard method in the art for measuring cell cycle effects and alterations.

As noted above, the lack of sensitivity of the MTT assay with respect to DNOS and possible AD patient groups may be due to the possible inclusion in these groups of individuals having disease conditions (other than AD) that affect mitochondrial function. This does *not,* however, affect the validity of the inventor's finding of the existence of the G1/S regulatory defect by alternative methods, such as flow cytometry. Based on the results of the experiments shown in Figure 2, the skilled artisan would conclude that one can directly differentiate AD patients from those suffering from other dementias using flow cytometry to assess G1/S transition control.

Applicant traverses the rejection under 35 U.S.C. § 112, first paragraph because the above-identified claims are supported by the Applicant's disclosure as of the filing date sought, demonstrated that the Applicant was in possession of the invention, and that the invention, in that context, is whatever is now claimed. The applicant showed possession of the claimed invention by describing the claimed invention with all of its limitations using descriptive means as words, figures, and diagrams that fully set forth the claimed invention. Specifically, the Applicant provided support in the specification as originally filed for claims drawn to a method of screening patients for Alzheimer's disease (AD) where the presence of

a G1/S checkpoint defect in non-neuronal cells indicates that the patient has AD. (Office Action at ¶ 13). That is the Applicant provides sufficient information regarding the subject matter of the claims to support the conclusion of one of ordinary skill in the pertinent art that that the cell cycle defect observed in the present studies is due to a G1/S checkpoint defect. Accordingly, the Applicant respectfully requests reconsideration and withdrawal of the 35 U.S.C. § 112, first paragraph rejections for lack of written description.

35 USC 112, first paragraph - Enablement

The Examiner rejected claims 1-6 and 11-12 pursuant to 35 U.S.C. § 112, first paragraph as non-enabled due to over breadth. Specifically, the Examiner alleges that, while the specification enables identifying a human subject who is likely to have AD by screening for a cell cycle defect in lymphocytes, the specification does not reasonably enable the diagnosis of AD in a human subject using any non-neuronal cell. That is, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the above-referenced claims. The Applicant traverses the Examiner's rejection of claims 1-6 and 11-12 pursuant to 35 U.S.C. §112, first paragraph because having demonstrated in the instant application that the cell cycle regulatory defect is present in one type of non-neuronal cell, namely lymphocytes, it is reasonable for one skilled in the art to conclude that the same regulatory defect will be present in other non-neuronal cell types and that such cell types may be determined without undue experimentation. Office Action at ¶¶ 18-19 and 25-27.

The Examiner alleges that "the skilled artisan would be unable to practice the full scope of the claimed invention without engaging in an undue level of non-trivial experimentation." Office Action at ¶ 27. The Applicant respectfully disagrees with the Examiners position as the test of enablement is not whether any experimentation is necessary or even "non-trivial", but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Even if the experimentation were complex it does not necessarily make it undue, where the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'd. sub nom., *Massachusetts Institute of Technology v. A.B Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35

U.S.C. 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Failure to disclose other methods by which the claimed invention may be made does not render a claim invalid under 35 U.S.C. 112. *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1533, 3 USPQ2d 1737, 1743 (Fed. Cir.), cert. denied, 484 U.S. 954 (1987). As discussed above, the Applicant has provided teachings that a regulatory defect at G1/S in AD patients cells is present in select non-neuronal cells, *e.g.*, lymphocytes, and disclose methods of diagnosis based on this teaching. The approach disclosed utilized experimental techniques known in the art and applicable to determine the utility of other non-neuronal cells in the methods of the invention.

In *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement), the court noted that there was no disagreement as to the facts, but merely a disagreement as to the interpretation of the data and the conclusion to be made from the facts. *In re Wands,* 858 F.2d at 736-40, 8 USPQ2d at 1403-07. The Court held that the specification was enabling with respect to the claims at issue where "there was considerable direction and guidance" in the specification; there was "a high level of skill in the art at the time the application was filed;" and "all of the methods needed to practice the invention were well known." 858 F.2d at 740, 8 USPQ2d at 1406. After considering all the factors related to the enablement issue, the court concluded that "it would not require undue experimentation to obtain antibodies needed to practice the claimed invention." *Id.*, 8 USPQ2d at 1407. The instant case is similar to *Wands* as there was a high level of skill in the art at the time the application was filed and the methods required to practice the invention were known in the art. That is, it would not be undue experimentation for the skilled artisan to assess other non-neuronal cell types from AD patients for a regulatory defect at G1/S as a means to determine their utility in the diagnostic methods of the instant application. As such, the claimed invention is enabled by the specification as it would not require the skilled artisan to engage in an undue level of experimentation to practice the full scope of the invention.

In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to

doubt the objective truth of the statements contained therein which must be relied on for enabling support. The Examiner raises questions regarding the correlation between the cell cycle defect identified in AD patients and Alzheimer's disease. Office Action at ¶¶ 21-25. As detailed below, the Examiner fails to meet his burden under 35 U.S.C. § 112, first paragraph as the Examiner's rationale is flawed and there is no reason to doubt the objective truth of the statements disclosed in the specification which are relied on by the Applicant for enabling support. As such, the rejection of the of above-referenced claims for lack of enablement due to over breath is improper.

The Examiner alleges that to "diagnose a disease" essentially means to determine a disease state that is causing a patient's symptoms. (Office Action at ¶ 21). The applicant maintains that this view of diagnosis is overly simplistic. In modern medicine persons skilled in the art strive to detect a disease before any symptoms appear using screening methods in populations "at risk." The population at risk in the case of AD is the population above 55-60 years of age. At this age the screening of lymphocytes for cell cycle regulatory defect at G1/S indeed allows the selection of the group which will later develop AD if left untreated. Although the examiner himself seems to agree that the specification provides sufficient information to enable one skilled in the art to screen lymphocytes for a cell cycle defect and definitively inform a patient that they have or will soon develop AD, he contends that no "true correlation" has been shown because the diagnosis of AD can only be made at post mortem. Notwithstanding the fact that every diagnostic method known in the art has some level of failure, the diagnostic criteria used to identify AD for inclusion in the inventor's experiments (NINCDS-ARDRA criteria) has been shown to have a 98-100% specificity for AD when followed up by post-mortem examination. Since the inventor has shown that the presence of cell cycle regulatory defects at G1/S correlates with a diagnosis of AD and preAD assessed by the NINCDS-ARDRA criteria, it can be inferred that the definition of AD (as used in the present application) can be relied upon in 98-100% of cases and enables selection of AD patients before classical symptoms have developed.

The problem with prior art methods of "diagnosing" AD based on assessment of patient symptoms is that the accepted NINCDS-ARDRA criteria diagnose the disease based on symptoms at a stage where nothing can be done in terms of therapeutic intervention to help the patient any more. It is thus extremely important for the benefit of asymptomatic AD patients to provide a screening method, such as that provided by the current invention, that will allow identification of patients before they have developed the terrible symptoms which allow diagnosis using the traditional criteria, at a stage where therapeutic intervention aimed at preventing or slowing development of AD pathology may still be possible.

The Examiner questions whether the detection of a cell cycle regulatory defect at the G1/S transition is necessarily indicative of AD? Office Action at ¶ 22.. Detection of this cell cycle regulatory defect in at "at risk" population is indicative of AD, having regard to the results included in the study. The data clearly indicate this for the reasons given above.

The Examiner interprets the introductory passages on pages 2 and 3 of the specification as indicating that the development of AD may be due to inappropriate re-entry of neurons into the cell cycle. In fact, this is only half of the story. In the inventor's opinion, AD is due to inappropriate re-entry of neurons into the cell cycle, *followed by a regulatory failure at the G1/S transition point*. Aberrant cell cycle re-entry alone is not sufficient for development of AD, as in healthy individuals this would be followed by cell cycle arrest and re-differentiation (see page 2, line 23-25.

The examiner also states that "if AD patients have symptoms that are reflected in somatic cells, it would certainly be plausible that other neurological disorders also show characteristics in non-neuronal cells". This statement is inaccurate for a number of reasons. First, the detection of the G1/S regulatory failure in somatic cells of AD patients does not mean that these patients have "symptoms" as this term would be normally understood by one skilled in the art. A "symptom" is some abnormality that the patient detects and it causes him to go to the doctor. Patients do not detect any abnormality as a result of the existence of the cell cycle defect in non-neuronal cells.

The failure of the G1/S regulatory checkpoint will not cause any detectable problems (let alone symptoms) in lymphocytes or in any other cells that naturally divide. The cells that generate lymphocytes are dividing populations. The peripheral lymphocytes are generated by division and when they do their job they are killed and replenished again by division. So in order to function properly a lymphocyte or its precursors does NOT need to rely on the G1/S transition checkpoint. It is not needed for its normal function and life cycle. This is why it is necessary to use artificial experimental procedures to force lymphocytes to use the G1/S checkpoint, so that the defect therein can be detectable. Having a broken G1/S control is somewhat analogous to having a bicycle with a broken brake. One can happily go around on the bicycle on a flat terrain. However, when one tries to negotiate a steep mountain-side with the same bicycle down-hill the broken brake will cause a major problem.

A neurological disorder will be associated with characteristic alterations in non-neuronal cells *only if the nature of the neuronal disease can manifest itself in non-neuronal cells*. If the neurological disorder is caused by a protein or system present in and utilised by non-neuronal cells then one can detect the problem from the periphery. The inventor has observed that this is

the case in AD, because the G1/S regulatory machinery is exactly the same in every cell of the body. Even if this regulatory mechanism is not used by cells for their normal life, they can be forced under artificial experimental conditions to utilise the system, and it is precisely such "forcing" of non-neuronal cells to manifest the G1/S defect which is present, but not normally detectable, which forms the basis of the inventors diagnostic screen.

The examiner also contends that cyclin expression and improper cell cycle re-entry is not restricted to AD (based on the inventors own paper), therefore the method provided by the invention would identify other patient groups such as epilepsy, Pick's disease and TLE patients as well as cancer patients. The examiner seemingly equates "cyclin expression" and "cell cycle re-entry" with "G1/S regulatory failure". In response, the inventor strongly submits that these terms describe different things and should be distinguished. The invention does not detect or analyse mere cell cycle re-entry (which is not specific for AD). Rather, the invention detects the G1/S regulatory failure which is specific to AD in the population at risk (above the age of 55-60). In response to the specific point raised in paragraph 23, as discussed above the anomalous results observed with DNOS patients in the MTT proliferation assay are not indicative of the presence of a G1/S defect, but rather reflect the inclusion in this patient group of individuals with disease conditions other than AD which affect mitochondrial function.

Applicant traverses the rejection under 35 U.S.C. § 112, first paragraph because the the specification does enable the diagnosis of AD in a human subject using any non-neuronal cell. That is, the specification enables any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the above-referenced claims. Specifically, he Applicant traverses the Examiner's rejection of claims 1-6 and 11-12 pursuant to 35 U.S.C. § 112, first paragraph because having demonstrated in the instant application that the cell cycle regulatory defect is present in one type of non-neuronal cell, namely lymphocytes, it is reasonable for one skilled in the art to conclude that the same regulatory defect will be present in other non-neuronal cell types and that such cell types may be determined without undue experimentation. Office Action at ¶¶ 18-19 and 25-27. It would not be undue experimentation for the skilled artisan to assess other non-neuronal cell types from AD patients for a regulatory defect at G1/S as a means to determine their utility in the diagnostic methods of the instant application. As such, the claimed invention is enabled by the specification as it would not require the skilled artisan to engage in an undue level of experimentation to practice the full scope of the invention. Also, the Examiner fails to meet his burden under 35 U.S.C. § 112, first paragraph as

there is no reason to doubt the objective truth of the statements disclosed in the specification which are relied on by the Applicant for enabling support. Accordingly, the Applicant respectfully requests reconsideration and withdrawal of the 35 U.S.C. § 112, first paragraph rejections for lack of enablement.

Claim Rejections -35 U.S.C. § 102-Anticipation

The Examiner rejected claims 1-6 and 11-12 under 35 U.S.C. §102(a) as allegedly anticipated by Nagy-b. *Neurosci. Lett.* 317:81-84 (2002). The Examiner's rejection pursuant to 35 U.S.C. §102(a) is moot as the Applicant provides herewith a certified copy of GB 0106051.6 application pursuant to the requirement of 35 U.S.C. § 119(b) to perfect their foreign priority claim. The Applicant asserts that the specification of GB 0106051.6 application provides sufficient support the invention as claimed. Accordingly, the Applicant respectfully requests reconsideration and withdrawal of the 35 U.S.C. § 102(a) rejections for anticipation.

CONCLUSION

On the basis of the foregoing amendments, Applicants respectfully submits that the pending claims are in condition for allowance and respectfully request the same. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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APPENDIX